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REMARKS

Claims 1-20 remain pending. Claims 1-4 and 20 are under Active Examination. Claims 5-19 are withdrawn from consideration.

The rejection of Claims 1-4 and 20 under 35 U.S.C. §103(a) over Quarto di Palo et al., The International Journal of Artificial Organs, Vol. 1, No. 1, 1978, pp. 112-113, is respectfully traversed. Quarto di Palo et al. fail to suggest the claimed method.

Applicants previously submitted an executed Declaration Under 37 C.F.R. §1.132 from Professor Adolf Grünert. Applicants have also submitted English translations of Gruenert et al., Infusiontherapie, Vol. 11, No. 1, February 1984 and Gruenert et al., Anasthesist, Vol. 33, No. 1, pp. 11-19, January 1984, for the Examiner's consideration. Those references were cited in the Declaration.

As set forth in his Declaration, Professor Grünert is the Medical Director and Chairman, Institute of Clinical Chemistry, University Hospital, Robert Koch-Str. 8, D-89070 Ulm in Germany. See paragraph 1 of the Declaration, and the copy of his Curriculum Vitae attached to the Declaration. Professor Grünert is an inventor in the present application.

As stated by Professor Grünert, the field of the invention of the present application is compositions suitable for hemodialysis. See paragraph 5 of the Declaration. Based on his years of experience working in the field of the invention, Professor Grünert considers himself an expert in that field. See paragraph 6 of the Declaration.

Professor Grünert has read and is familiar with the present application, including the claims of that application. He has also read the Official Action dated December 17, 2002 in the present application and Quarto di Palo et al. See paragraphs 7-9 of the Declaration.

At page 112, column 2, lines 9-11 of text under "Sir," Quarto di Palo et al. state:

> we have tried adding amino acids to the dialysis solution in a concentration equal to that of normal plasma.

According to Professor Grünert, the dialysis solution described by Quarto di Palo et al. does not contain the complete pattern of amino acids present in normal plasma. The dialysis solution described by Quarto di Palo et al. is missing Gln, Tyr, Cys, Asn, and Cit, all of which are present in normal plasma. See paragraphs 10 and 11 of the Declaration.

According to Professor Grünert , in 1978, when Quarto di Palo et al. was published in the scientific literature, the complete amino acid composition of normal plasma was well-known in the art. That this is so is demonstrated by Meister, A. (ed.), Biochemistry of the Amino Acids, Second Edition, Vol. 1, pp. 110 (1965). A copy of pages 108-117 of that reference text is attached hereto. See paragraph 12 of the Declaration.

In addition, Professor Grünert points out the Table at the top of page 113 of Quarto di Palo et al. explicitly states that Cit (citrulline), Cys (cystine), and Tyr (tyrosine) are present in normal plasma at a specified range, but are not present in the dialysis solution described in that reference. See paragraph 13 of the Declaration.

In Professor Grünert's opinion, at the time the present application was filed in 1999, one of ordinary skill in the field of the invention would have interpreted Quarto di Palo et al. to suggest that if an amino acid is used in the dialysis solution, then it should be used at a concentration in the range for normal plasma. See paragraph 14 of the Declaration.

Significantly, Professor Grünert points out, that since the amino acids Gln, Tyr, Cys, Asn, and Cit were not used by Quarto di Palo et al., and those amino acids were well-known as components of normal plasma at the time that reference was published, one of ordinary skill in the field of the invention reading that reference at the time the present application was filed in 1999 would have concluded that Quarto di Palo et al. did not consider those amino acids to be useful components of a dialysis solution, even though they were known

components of normal plasma. Otherwise, according to Professor Grünert, Quarto di Palo et al. would have used those amino acids in the dialysis solution described in that reference. See paragraph 15 of the Declaration.

In view of the foregoing, in Professor Grünert's opinion, Quarto di Palo et al. would not have suggested to one of ordinary skill in the art in the field of the invention at the time the present application was filed in 1999 to modify the dialysis solution described by Quarto di Palo et al. by including Gln, Tyr, Cys, Asn, and Cit. According to Professor Grünert, this is because one skilled in the art would have recognized in 1999 that if Quarto di Palo et al. considered those amino acids to be useful components of a dialysis solution, then Quarto di Palo et al. would have included them in the dialysis solution described in that reference. Since those amino acids were well-known components of normal plasma in 1978 at the time that the Quarto di Palo et al. reference was published, the fact that Quarto di Palo et al. failed to use Gln, Tyr, Cys, Asn, and Cit would have been considered one of ordinary skill in the art in the field of the invention at the time the present application was filed in 1999 as a direct teaching away from the dialysis composition claimed in the present application. See paragraph 16 of the Declaration.

Professor Grünert notes that, as described in the specification of the present application at pages 1-2, patients with impaired kidney function have imbalanced amino acid compositions. See paragraph 17 of the Declaration. Professor Grünert points out that, as noted above, the dialysis solution described by Quarto di Palo et al. is based on the amino acid content of normal plasma. See paragraph 18 of the Declaration.

However, Professor Grünert points out that as described in the specification of the present application at page 2, administering such a solution to the patient actually exacerbates the amino acid imbalance in the patients. As a result, the dialysis method like that described by Quarto di Palo et al. has not been adopted for routine therapy, and has been evaluated as

too expensive and ineffective. That this is so is demonstrated by Tepper et al., The International Journal of Artificial Organs, Vol. 1, No. 4, 1981, pp. 208-210, a copy of which is submitted herewith. See paragraph 19 of the Declaration.

In Professor Grünert's opinion, the dialysis solution described by Quarto di Palo et al. has the following disadvantages as compared to the dialysis composition claimed in the present application:

> (a) the total concentration of the dialysis solution described by Quarto di Palo et al. is with 250 mg/L not sufficient to compensate for the concentration gradient of amino acids, and
>
> (b) the total concentration with 407 mg/L of the composition claimed in the present application is isotonic with respect to plasma amino acid concentrations in healthy people. See Grünert et al., Infusiontherapie, 11, 12-15 (1984) (hereinafter referred to as "Grünert et al. I") and Grünert et al., Anaesthesist, 33, 11-19 (1984) (hereinafter referred to as "Grünert et al. II").

See paragraph 20 of the Declaration. Copies of Grünert et al. I and II, as well as English translations of the same, are of record in this case.

The Examiner taken the position that there is no evidence that the statements in paragraph 20 of the Declaration are supported by the Grünert et al. references cited therein. Referring to Grünert et al. I, page 11 lines 31 et seq. of the English translation, the total concentration for males (2.86 mmol/L) and females (3.2 mmol/L) is described. The average of these two values is about 3.0 mmol/L. Since the average molecular weight of the amino acids in the blood is about 135 g/mol, this calculates to a value of 405 mg/L. A detailed

calculation taking into account the exact molecular weights provides the value of 407 mg/L stated in paragraph 20 of the declaration. A calculation based on the mixture described by Quarto di Palo et al. provides a value of only 250 mg/L, which is insufficient to solve the problem associated with parenteral nutrition. A copy of a letter from Dr. Grünert to the Applicant's representative in Germany (Dr. Retzow) and an English translation of the same discussing this point is attached.

Based on the foregoing, Quarto di Palo et al. fail to suggest the claimed method. Accordingly, Claims 1-4 and 20 are not obvious over that reference.

Applicants respectfully request that the obviousness-type double patenting rejection be held in abeyance until an indication of allowable subject matter in the present application. A suitable Terminal Disclaimer will be filed at that time.

Applicants submit that the present application is condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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[see original for letterhead information]

2 February 2004

U.S. Patent Application No. 09/769,397
"Amino acid composition for hemodialysis"
Ref.: 96041 AM

Dear Dr. Retzow:

The two cited works in § 20 of the declaration document the original data on concentrations and percentage compositions of the amino acids in the plasma of healthy human subjects (blood donors). These data represent the basis for the composition of the dialysate solution. The dialysate solution, which has physiological composition and thus is isotonic and thereby gradient-free relative to the individual amino acids, was prepared to correspond to these (our) published study results. A total concentration of 407 mg/ml is calculated from the micromolar concentrations.

On the basis of the values given for the mixture by Quarto di Palo et al. in the cited paper (Int. J. Artific. Organs (1981), Vol. 1, pp. 208-210), the proposed dialysate solution has a concentration of only 250 mg/l, which is not isotonic and therefore also not gradient-free relative to physiological plasma.

Best regards

[signature]

Ad Grünert

Professor Adolf Grünert
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U.S. Patent Application No. 09/769, .397
„Amino acid composition for hemodialysis"
Ref.: 96041 AM

Sehr geehrter Herr Dr. Retzow,

die beiden zitierten Arbeiten in § 20 der Deklaration dokumentieren die Originaldaten über die Konzentrationen und prozentualen Zusammensetzungen der Aminosäuren im Plasma gesunder Menschen (Blutspender), die die Grundlage für die Zusammensetzung der Dialysatlösung darstellen. Diesen eigenen, publizierten Untersuchungsergebnissen entsprechend wurde die physiologisch zusammengesetzte und damit in Bezug auf die einzelnen Aminosäuren isotone und dadurch gradientenfreie Dialysatlösung hergestellt. Aus den mikromolaren Konzentrationen errechnet sich eine Gesamtkonzentration von 407 mg/l.

Aufgrund der Mischungsangaben von Quarto di Palo et al. in der zitierten Arbeit Int. J. Artific. Organs (1981), Vol.1 pp 208-210 weist die vorgeschlagene Dialysatlösung nur eine Konzentration von 250 mg/ auf, die in Bezug auf das physiologische Plasma nicht isoton und damit auch nicht gradientenfrei ist.

Mit besten Grüßen

Ad Grünert

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